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Research Article

Comparing the efficacy of tadalafil and tamsulosin for managing erectile dysfunction and lower urinary tract symptoms in prostate brachytherapy patients: a prospective study

Nozomi Hayakawa [a, b], Ryuichi Mizuno [a, b], Tomoki Tanaka [c], Yutaka Shiraishi [c], Kazuhiro Matsumoto [a], Takeo Kosaka [a], Eiji Kikuchi [a, b], Mototsugu Oya [a, *]

[a] Department of Urology, Keio University, School of Medicine, Tokyo, Japan
[b] Department of Urology, St. Marianna University, School of Medicine, Kanagawa, Japan
[c] Department of Radiology, Keio University, School of Medicine, Tokyo, Japan

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ABSTRACT

Introduction: Adverse events, such as erectile dysfunction (ED) and lower urinary tract symptoms (LUTS), are significant concerns in prostate cancer (PCa) patients treated with Iodine 125 (I-125) low-dose rate (LDR) prostate brachytherapy (PB). Alpha antagonists and phosphodiesterase-5 inhibitors are used to manage these events. The present study compared the efficacy of low-dose tadalafil with that of tamsulosin for concomitant ED and LUTS in PCa patients treated with I-125 LDR PB.

Materials and methods: One hundred and seventeen patients who received PB for low- or intermediate-risk localized PCa were analyzed. They were randomized into two groups, one receiving tamsulosin ($N = 58$) and the other receiving low-dose tadalafil ($N = 59$) immediately after PB. Sexual and urinary functions were assessed at various time points post-PB using questionnaires and objective measurements. The primary endpoint was sexual function measured by the International Index of Erectile Function-15 (IIEF-15) EF domain scores 6 months after PB. Secondary endpoints were sexual function measured by total IIEF-15 scores and Erection Hardness Scores 6 months after PB. The exploratory endpoint was the LUTS status 6 months after PB.

Results: No significant differences were observed in baseline characteristics between the two groups. Tadalafil exerted stronger effects on sexual function, particularly erection hardness, than tamsulosin. No significant differences were observed in the management of LUTS between both treatments.

Conclusion: Low-dose tadalafil and tamsulosin may manage LUTS equally after PB. Low-dose tadalafil may contribute to the maintenance of erectile function, particularly erection hardness, after PB; therefore, it is a viable option for patients with baseline erectile function.

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1. Introduction

Patients with clinically localized prostate cancer (PCa) may be curatively treated with different modalities, such as radical prostatectomy, prostate brachytherapy (PB), and external beam radiotherapy (EBRT).[1] An increasing number of patients with low-risk PCa are currently under active surveillance. Among the treatment options available for localized PCa, iodine 125 (I-125) low-dose rate (LDR) PB is an effective and minimally invasive approach.[2] Factors that affect treatment decisions for localized PCa are complex. In

Abbreviations: (PCa), prostate cancer; (PB), prostate brachytherapy; (EBRT), external beam radiotherapy; (I-125), iodine 125; (LDR), low-dose rate; (QOL), quality of life; (ED), erectile dysfunction; (LUTS), lower urinary tract symptoms; (PDE-5), 5-phosphodiesterase; (EF), erectile function; (IIEF-15), International Index of Erectile Function-15; (EHS), Erection Hardness Score; (IPSS), International Prostate Symptom Score; (OABSS), Overactive Bladder Symptom Score; (Qmax), maximum urinary flow rate; (PVR), post-void residual urine; (CI), confidence interval.

* Corresponding author. Department of Urology, Keio University School of Medicine, Shinanomachi 35, Shinjuku-ku, Tokyo, 1608582, Japan.
E-mail address: moto-oya@keio.jp (M. Oya).

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addition to the anticipated cancer control rate, long-term changes in quality of life (QOL) are considered. Definitive therapy for PCa is often associated with adverse events, including urinary, sexual, and bowel dysfunction; however, recovery times are shorter with I-125 LDR PB than with other treatment modalities, such as prostatectomy.[3]

Among post-treatment adverse events, erectile dysfunction (ED) and lower urinary tract symptoms (LUTS) are two major concerns for PCa patients treated with I-125 LDR PB, and several medical treatments have been attempted for their control. Previous studies demonstrated that alpha antagonists, such as tamsulosin, naftopidil, and silodosin, recovered LUTS to baseline after PB.[4–6] Radiotherapy-induced ED appears to be attributed to a multifactorial process, including neurogenic compromise, vascular insufficiency, local trauma, and psychogenic causes, with microvascular damage representing the most dominant factor.[7] The early induction of 5-phosphodiesterase (PDE-5) inhibitors, such as sildenafil and tadalafil, has been attempted with the intention of preserving sexual QOL after treatments for PCa, including PB.[8,9] Therefore, PDE-5 inhibitors have historically been recommended for ED and alpha-1 blockers for LUTS for prophylactic or therapeutic purposes after PB.

Tadalafil is a PDE-5 inhibitor that induces smooth muscle relaxation in the bladder, urethra, and prostate via the nitric oxide/cyclic guanosine monophosphate/protein kinase G pathway. It also increases blood perfusion to the pelvic area by relaxing the smooth muscle of the surrounding vasculature, and modulates sensory stimuli from this area.[10] The recommended starting dose of tadalafil for ED is 10 mg, which is taken prior to anticipated sexual activity. In 2011, low-dose tadalafil was also approved for benign prostate hyperplasia by the US Food and Drug Administration; however, the exact mechanisms of action of PDE-5 inhibitors on LUTS remain unclear. Since daily treatment with low-dose tadalafil has been shown to improve sexual function, the European Association of Urology guidelines recommend it for patients with the comorbidities of LUTS and ED.[11]

Previous studies indicated the efficacy of tadalafil for the prevention and treatment of ED and/or LUTS caused by surgical/radiation therapy for PCa. The REACTT trial is a multicenter, randomized, placebo-controlled study that examined the effects of tadalafil on erectile function (EF) recovery in PCa patients who underwent nerve-sparing prostatectomy.[12] The findings obtained indicate that the administration of tadalafil 5 mg once daily early after prostatectomy contributed to EF recovery and the prevention of penile length loss. Furthermore, a *post hoc* analysis of this trial revealed the amelioration of urinary incontinence in elderly patients.[13] A randomized placebo-controlled clinical trial was also performed to confirm the efficacy of low-dose daily tadalafil for the prevention of ED after radiotherapy, including both EBRT and PB; however, EF was similar in the low-dose daily tadalafil and placebo arms.[14] Combination therapy with alpha antagonists and PDE-5 inhibitors is commonly used for treating LUTS after radiation therapy, including PB. However, when considering this combination therapy in terms of its effects on sexual function, it is important to note that while PDE-5 inhibitors have a mechanism that contributes to the improvement of sexual function, alpha-1 blockers are associated with side effects that impair sexual function, such as retrograde ejaculation. Since tadalafil is indicated for both ED and LUTS, if it proves effective in controlling both conditions after PB as a monotherapy, it would be considered advantageous not only for its efficacy but also for its management simplicity compared to combination therapy. The aim of the present study was to prospectively compare the efficacy of low-dose tadalafil monotherapy with that of tamsulosin monotherapy in managing both ED and LUTS in patients who received I-125 LDR PB for localized PCa.

2. Materials and methods

This was a prospective randomized study that compared tamsulosin hydrochloride ($N = 58$) with tadalafil ($N = 59$) in patients receiving PB for localized PCa to assess the efficacy of low-dose tadalafil for both ED and LUTS. The protocol was approved by the Institutional Ethics Committee (No. 20150053). Written informed consent was obtained from all patients given adequate information on this trial.

2.1. Patient population and study design

Patients scheduled for transperineal interstitial PB with I-125 seeds for low- or intermediate-risk localized PCa at our institution were eligible for this study. Patients who received additional EBRT and those already taking alpha-1 blockers or PDE-5 inhibitors before PB were excluded. Androgen deprivation therapy was permitted for 3 months before PB to achieve prostate volume reductions in order to meet the legal criteria for PB in Japan. After meeting the eligibility criteria and providing informed consent, participants were randomized into two groups: the daily administration of 0.2 mg of tamsulosin hydrochloride or 5 mg of tadalafil just after PB (Supplement Fig. 1). The duration of the study was 12 months and the sexual and urinary functional status of patients was assessed at baseline and 1, 3, 6, and 12 months after PB. The sexual and EF status was evaluated using the Japanese version of the International Index of Erectile Function-15 (IIEF-15) questionnaire,[15] particularly the EF subdomain, and the Erection Hardness Score (EHS). The severity of ED was categorized into the following 5 groups by the EF domain score: severe, 10 or less; moderate, 11 to 16; mild to moderate, 17 to 21; mild, 22 to 25; and none, 26 or higher.[16] To assess the severity of LUTS, including incontinence, irritability, and difficulty, the International Prostate Symptom Score (IPSS), the Overactive Bladder Symptom Score (OABSS), maximum urinary flow rate (Qmax), and post-void residual urine (PVR) were utilized. The IPSS comprises seven questions, with the total IPSS being the sum of each score. In addition, the IPSS was divided into three subscores: a storage subscore (questions 2, 4, and 7), a voiding subscore (questions 3, 5, and 6), and a post-voiding subscore (question 1). The sum of each subscore was also analyzed.

2.2. Endpoints and definitions

The primary study endpoint was sexual function measured by the IIEF-15 EF domain score 6 months after PB. Secondary endpoints were sexual function measured by total IIEF-15 scores and EHS 6 months after PB. Exploratory endpoints were the LUTS status 6 months after PB was evaluated by IPSS, QOL, OABSS, Qmax, and PVR.

2.3. PB protocol

Prostate volume was measured using transrectal ultrasound (TRUS) approximately 1 month before the procedure. The planning target volume was defined as the prostate itself. The prescribed dose was set at 160 gray (Gy). All patients underwent TRUS-guided transperineal I-125 radioactive-free seed implantation using an applicator ($N = 60$, Mick Radio-Nuclear Instruments, New York City, NY, USA) or intraoperatively built custom-linked seeds ($N = 57$). Intraoperative dynamic planning and seed placement were performed using biplanar TRUS imaging by the standard technique with a peripheral loading pattern. In 20 cases, a spacer material was injected after the completion of the PB implant. Postimplant pelvic computed tomography was conducted 4–6 weeks after PB using 5-mm spacing between images. Contoured images and sources were

entered into a Varian VariSeed treatment planning system (Varian, Charlottesville, VA). In addition, D90 (the minimum dose covering 90% of the prostate volume), V100 (the fractional prostate volumes receiving 100% of the prescribed dose), and urethral and rectal volumes receiving 150% and 100% of the prescribed dose were calculated.

2.4. Statistical analysis

Continuous variables are presented as a median with a range and a mean with a 95% confidence interval (CI). The present study had a small sample size and strong evidence suggested non-normality based on the results of the Shapiro-Wilk test; therefore, data were analyzed using non-parametric tests. Variables in different groups were compared using the Mann-Whitney U test and changes over time in each score in the same groups were examined using the Wilcoxon signed rank test. Categorical variables in characteristics were tested using a chi-square test. Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) software version 24 (Chicago, IL, USA). In all comparisons, the significance level was set to $P < 0.05$.

3. Results

3.1. Patient characteristics

Between July 2015 and August 2020, 117 participants were enrolled in the present study. The baseline characteristics of 117 eligible participants (59 in the tamsulosin group and 58 in the tadalafil group) and dosimetric parameters for PB are shown in Table 1. No significant differences were observed in baseline parameters between the two groups. Out of the 59 participants in the tamsulosin group, 51 (86.4%) completed 6 months of treatment, while 51 out of the 58 participants in the tadalafil group (87.9%) did the same. Ultimately, 47 participants in the tamsulosin group (79.7%) and 48 participants in the tadalafil group (82.8%) completed the entire treatment protocol (Supplement Fig. 1).

3.2. Effects of tamsulosin and tadalafil on sexual function

Results on sexual function at baseline and 1, 3, 6, and 12 months after PB in the tamsulosin and tadalafil groups are summarized in Table 2. At baseline and 1 month after PB, no significant differences were observed in scores for total IIEF-15 and the EF domain between the groups, whereas 3 months after PB, scores for total IIEF-15 and the EF domain were significantly higher in the tadalafil group than in the tamsulosin group. At 6 months, scores for the EF domain, the primary endpoint of the present study, were significantly higher in the tadalafil group, whereas no significant difference was observed in those for total IIEF-15. At 12 months, no significant differences were noted in scores for total IIEF-15 or the EF domain between the groups. Moreover, EHS at baseline and 1 month after PB did not significantly differ; however, it was significantly higher in the tadalafil group than in the tamsulosin group 3, 6, and 12 months after PB. These results imply that tadalafil achieved erection hardness and early recovery of sexual function after PB.

Fig. 1 shows a box-and-whisker plot of time course changes in scores for total IIEF-15, EF domain, and EHS. Total IIEF-15 scores were significantly lower 1 month after PB than at baseline in both groups. At 3 months, the tamsulosin group still showed a significant decrease from baseline, whereas the tadalafil group showed an improvement. At 6 and 12 months, no significant decrease from baseline was observed in either group (Fig. 1A). EF domain scores were significantly lower 1 and 3 months after PB than at baseline in both groups. At 6 months, the tamsulosin group still showed a significant decrease from baseline, whereas the tadalafil group showed an improvement. No significant change from baseline was observed in either group at 12 months (Fig. 1B). EHS was significantly lower 1, 3, and 6 months after PB than at baseline and then recovered at 12 months in the tamsulosin group. On the other hand, EHS was maintained after PB in the tadalafil group (Fig. 1C). The time course changes in IIEF-15, EF domain, and EHS in the groups receiving and not receiving androgen deprivation therapy for 3 months prior to PB are shown in Supplement Table 1. In both groups, recovery of the EF domain after PB was faster in the tadalafil group. Furthermore, regardless of androgen deprivation therapy, EHS in the tadalafil group did not show a significant decrease from baseline and was maintained.

3.3. Effects of tamsulosin and tadalafil on subjective and objective LUTS findings

Details for subjective and objective LUTS findings at baseline and 1, 3, 6, and 12 months after PB in the tamsulosin and tadalafil groups are summarized in Supplement Table 2. No significant

Table 1
Patient characteristics

Baseline parameters	Tamsulosin $N = 58$	Tadalafil $N = 59$	P value
Age median (range), y	68.1 (51-79)	68.0 (51-81)	0.827
PSA, median (range), ng/ml	6.0 (3.0-19.8)	7.2 (3.2-13.6)	0.165
PV, median (range), ml	25.0 (11.5-42.1)	26.0 (14.5-36.0)	0.832
Gleason score			0.489
3 + 3, *n* (%)	9 (15.5)	5 (8.5)	
3 + 4, *n* (%)	28 (48.3)	30 (50.8)	
4 + 3, *n* (%)	21 (36.2)	24 (40.7)	
T stage			0.878
1c, *n* (%)	18 (31.0)	21 (35.6)	
2a, *n* (%)	30 (51.7)	28 (47.5)	
2b, *n* (%)	1 (1.7)	0 (0)	
2c, *n* (%)	9 (15.6)	10 (16.9)	
Dosimetric parameters			
Seed median (range), piece	65.5 (48-91)	65.0 (51-83)	0.670
V100 median (range), %	96.8 (79.5-99.9)	96.8 (73.9-99.9)	0.987
D90 median (range), Gy	185.1 (142.4-209.8)	186.3 (139.9-214.2)	0.524
Urothelial V150 median (range), cc	0.00 (0.00-0.30)	0.01 (0.00-0.56)	0.263
Rectal V100 median (range), cc	0.22 (0.00-2.92)	0.23 (0.00-1.74)	0.528

PV: prostate volume.

Table 2
Effects of tamsulosin and tadalafil on sexual function

	IIEF	Tamsulosin	Tadalafil	*P* value
		mean (median)	mean (median)	
baseline	Total	21.8 (12.5)	26.6 (16.0)	0.259
	EF domain	7.4 (3.0)	9.9 (4.0)	0.279
1 month	Total	14.8 (11.0)	17.0 (11.0)	0.407
	EF domain	3.7 (2.0)	5.4 (3.0)	0.138
3 months	Total	15.8 (10.0)	23.3 (14.0)	*0.013
	EF domain	4.5 (2.0)	8.3 (4.0)	*0.009
6 months	Total	17.7 (11.0)	24.5 (15.5)	0.076
	EF domain	5.3 (2.0)	9.3 (4.0)	*0.021
12 months	Total	19.9 (15.0)	28.3 (15.5)	0.179
	EF domain	6.6 (5.0)	10.7 (5.0)	0.141
	EHS			
baseline	Total	1.82 (2.0)	2.12 (2.0)	0.323
1 month	Total	1.34 (1.0)	1.85 (2.0)	0.085
3 months	Total	1.35 (1.0)	2.26 (2.0)	*0.001
6 months	Total	1.35 (1.0)	2.18 (2.0)	*0.004
12 months	Total	1.57 (1.0)	2.23 (2.0)	*0.019

IIEF: International Index of Erectile Function, EF: Erectile Function.
EHS: Erection Hardness Score.
*$P < 0.05$.

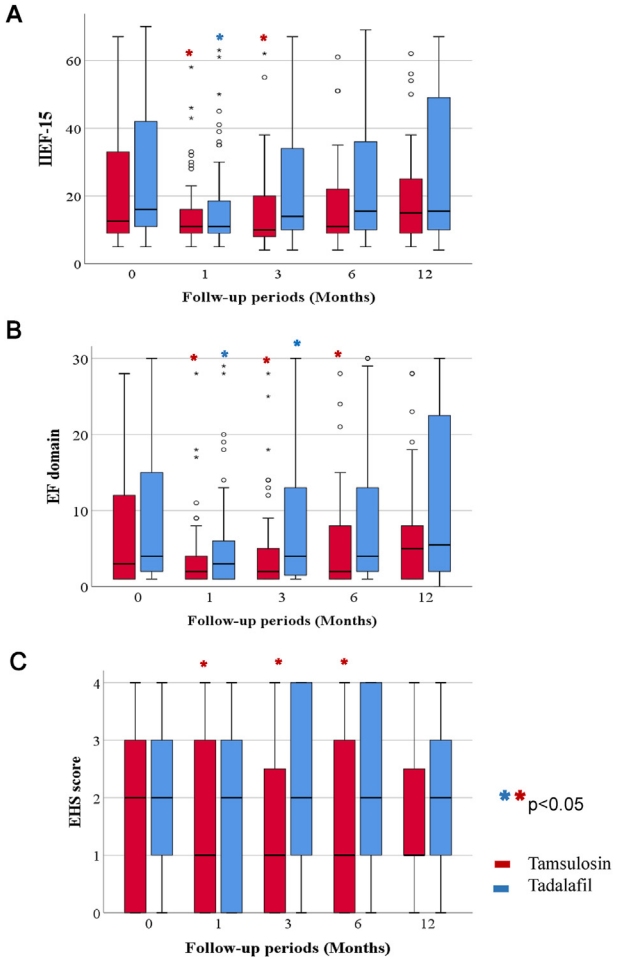

Figure 1. Comparison of assessments of sexual functions before and after PB between tadalafil and tamsulosin groups (*$P < 0.05$). (A) IIEF-15 (B) IIEF-15 EF domain (C) EHS IIEF-15: International Index of Erectile Function-15, EF: Erectile Function, EHS: Erection Hardness Score (EHS).

differences were observed in IPSS, QOL, OABSS, Qmax, or PVR between the groups.

Fig. 2 shows box-and-whisker plots of subjective and objective LUTS findings at baseline and 1, 3, 6, and 12 months after PB in the tamsulosin and tadalafil groups. All subjective LUTS findings, including IPSS, QOL, and OABSS, were significantly lower 1, 3, and 6 months after PB than at baseline in both groups ($P < 0.05$). At 12 months, IPSS, QOL, and OABSS recovered to baseline in both groups (Fig. 2A, B, C). Among objective LUTS findings, Qmax was significantly lower 1, 3, 6, and 12 months after PB than at baseline in both groups ($P < 0.05$). PVR was significantly higher 1 and 3 months after PB than at baseline in the tamsulosin group, whereas no significant increase was noted in the tadalafil group (Fig. 2D and E).

3.4. Endpoints and assessments

EF domain scores 6 months after PB, the primary endpoint of this study, were significantly higher in the tadalafil group than in the tamsulosin group ($P = 0.021$, Table 2). No significant differences were observed in total IIEF-15 scores 6 months after PB, a secondary endpoint of this study, between the groups ($P = 0.076$, Table 2); however, EHS 6 months after PB, another secondary endpoint of this study, were significantly higher in the tadalafil group than in the tamsulosin group ($P = 0.004$, Table 2). No significant differences were noted in subjective or objective LUTS findings, including IPSS, QOL score, OABSS, Qmax, and PVR, 6 months after PB.

4. Discussion

PB was initially introduced in 2003 in Japan and is now recognized as one of the curative treatment modalities for localized PCa. Since PB offers long-term survival, the control and monitoring of QOL after PB has been the focus of research. LUTS and ED are frequent adverse events of PB that affect the QOL of patients. To manage these adverse events and maintain good overall QOL, various medical interventions have been attempted. In the present study, we prospectively compared the effects of low-dose daily tadalafil on sexual and urinary functions with those of tamsulosin

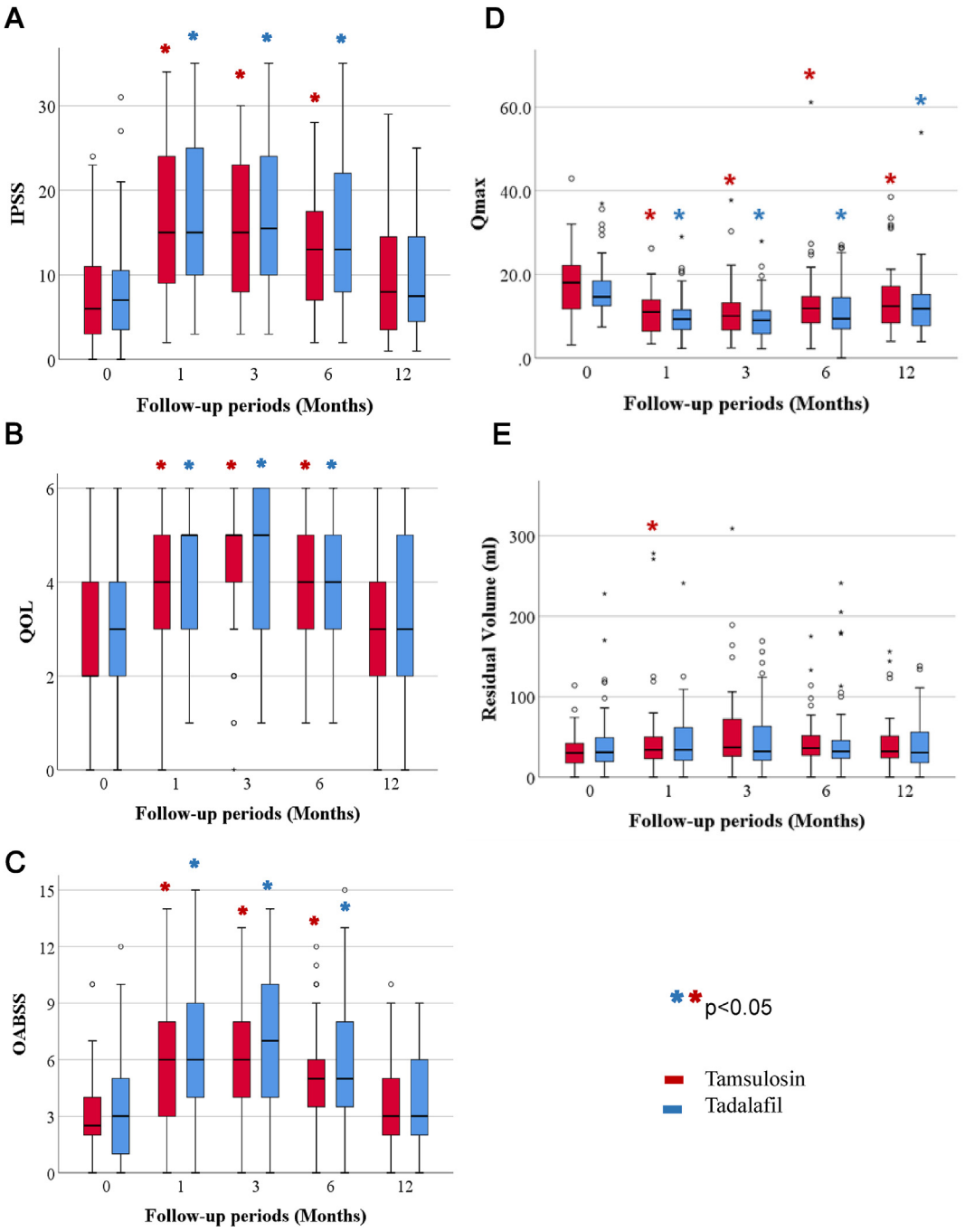

Figure 2. Comparison of assessments of urinary functions before and after PB between tadalafil and tamsulosin groups (*$P < 0.05$). (A) IPSS (B) QOL score (C) OABSS (D) Qmax (E) Residual volume. IPSS: International Prostate Symptom Score, QOL: quality of life, OABSS: the Overactive Bladder Symptom Score, Qmax: maximum urinary flow rate.

in patients with localized PCa treated with PB at our single center. The results obtained indicated no significant differences in the majority of urinary parameters between the two groups, whereas tadalafil exerted stronger effects on sexual function, particularly erection hardness.

The use of alpha-1 blockers, such as tamsulosin, naftopidil, and silodosin, is regarded as a standard treatment for the management of LUTS after PB, particularly when these symptoms are related to urinary obstruction or irritative symptoms.[17] PDE5 inhibitors, including tadalafil, increase blood flow to organs, which results in prostate tissue oxygenation and improves endothelial function as well as prostate inflammation. Since ionizing radiation may result in direct tissue damage, the effective control of LUTS after PB by low-dose tadalafil was expected. Minagawa et al previously reported that low-dose tadalafil and tamsulosin exerted similar effects on LUTS after PB.[18] In the present study, no significant differences were observed in any questionnaires for LUTS or objective examinations between the two groups and, thus, low-dose tadalafil monotherapy is considered to have the ability to manage LUTS after PB, comparable to tamsulosin.

The efficacy of tadalafil for ED after radiotherapy for PCa has not been demonstrated.[14] In the present study, the effects of low-dose

tadalafil on sexual function were mixed, namely, modest effects on the EF domain in IIEF-15 and better effects on EHS than in the tamsulosin group. The exact cause of ED after PB may be multifactorial; however, damage to the vasculature in erectile tissue around the prostate is known to reduce blood flow to erectile tissues, making it difficult to achieve and maintain an erection.[19] We consider the PDE5 inhibitor tadalafil to contribute to the maintenance and improved erection hardness after PB because it induces the relaxation of arterial and trabecular smooth muscle, leading to arterial dilatation, venous constriction, and erection. We speculate that a lower baseline IIEF score, an issue that is specific to Japanese patients, negatively affected the study results. Marumo et al reported a higher prevalence of moderate and severe ED in male Japanese patients older than 60 years.[20] Okihara et al evaluated sexual function in Japanese patients treated with PB and found that 46.3% had no sexual activity, while 34.6% had no sexual desire for erection at baseline.[21] In the present study, 69% of patients were categorized as having severe ED at baseline. Since IIEF-15 is a questionnaire that requires a certain level of sexual activity, we speculate that a lack of sexual activity inevitably resulted in a low baseline score. Therefore, EHS, which is not affected by the degree of sexual activity,[22–24] is more appropriate than IIEF-15 for assessing EF in sexually inactive middle-aged and elderly Japanese males.

There are several limitations that need to be addressed. The study population was small. Moreover, not all of the participants had active sexual function. While excessive radiation to the prostate apex area may affect the preservation of EF after PB, the present study did not thoroughly assess radiation doses in specific anatomical structures, such as the neurovascular bundle, penile bulb, crura, and corpus cavernosum, which are important for understanding the impact on potency. Furthermore, since this study was conducted for 1 year after PB, the long-term effects of low-dose tadalafil and tamsulosin on ED/LUTS after PB remain unknown. Nevertheless, the results obtained herein provide practical information because no other studies have evaluated the effects of low-dose tadalafil on ED after PB using EHS.

In conclusion, low-dose tadalafil may contribute to the maintenance of EF, particularly in terms of erectile hardness, after PB. Based on the results of this study, tadalafil could be considered the preferred supportive medication as the initial monotherapy for patients treated with PB, especially those with preserved sexual function. Additionally, for patients whose primary concern is LUTS, tadalafil might be sufficient, as it has demonstrated similar effectiveness to tamsulosin.

Ethics approval and consent to participate

Ethical approval of this study was approved by the Keio University School of Medicine Ethics Committee (https://www.ctr.med.keio.ac.jp/rinri/). All procedures performed in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all patients (Approval No 20150053, Ethics Committee of Keio University).

Consent for publication

Informed consent for publication was obtained in written form. No one declined.

Availability of data and materials

The data that support the findings of this study are not publicly available on ethical ground but are available from the corresponding author with permission from the Keio University School of Medicine Ethics Committee.

Author contributions

N. Hayakawa analyzed and interpreted the data, and drafted the manuscript. R. Mizuno carried out the design of this research. T. Tanaka, Y. Shiraishi, K. Matsumoto, and T. Kosaka participated in the collection of data and data analysis. E. Kikuchi and M. Oya assisted in the design of this research and project development. All authors read and approved the final manuscript.

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None.

Conflicts of interest

All authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prnil.2024.09.004.

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